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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,225	09/18/2000	Mary Lynne Hedley	08191/013001	4277

26161 7590 07/03/2003

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/03/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/664,225	Hedley
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 21, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-44, 46-62, 64-66, and 68-77* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-44, 46-62, 64-66, and 68-77* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Sep 18, 2000* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *16*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 21, 2003 has been entered.

Claims 60, 64-66 have been amended; Claims 45, 63, 67 have been canceled; claims 70-77 have been added by the amendment filed April 21, 2003.

Elected claims 1-44, 46-62, 64-66, 68-77, drawn to a hybrid DNA encoding multiple epitope(s) of viral antigens, method of virally infected treatment by DNA applications including humans patient suffering from, or at risk of a condition selected from the group consisting of exophytic condyloma, flat condyloma, cervical cancer, respiratory papilloma, conjunctival papilloma, genital-tract HPV infection, cervical dysplasia, high grade squamous intraepithelial lesions, and anal HPV infection, are pending for examination.

The examiner acknowledges the telephone interview held between Jack Brennan and the examiner on April 16, 2003. During the interview, the examiner acknowledges that should claims 63-66 be rewritten in independent form to include all of the limitations of the base claims, the claims are in condition for allowance. However and to the extent that the as-filed application still claims particular claimed embodiments, drawn to method of virally infected treatment by DNA applications including humans patient suffering from, or at risk of a condition selected from the group consisting of exophytic condyloma, flat condyloma, cervical cancer, respiratory papilloma, conjunctival papilloma, genital-tract HPV infection, cervical dysplasia, high grade squamous intraepithelial lesions, and anal HPV infection, the claims that clearly embrace such claimed embodiments, remain and/or are rejected for the same ground of the rejection under 35 USC 112, first paragraph, as set forth in the final office action dated January 16, 2003. As such, the examiner notes while applicant's claimed invention is found enabling for a number of mammals other than humans such as pigs and small mammals, the claimed invention is not reasonably enabling for applicability in human patients suffering or at risk from a viral infection and/or cancer, *e.g.,* hepatitis, HIV and HPV infection, exophytic condyloma, flat condyloma, cervical cancer, respiratory papilloma, conjunctival papilloma, genital-tract HPV infection, cervical dysplasia, high

grade squamous intraepithelial lesions, wherein these claimed embodiments are clearly embraced by the claimed invention. As the result, the ground of the rejection for claims drawn to human patients is set forth as follows:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-62, 64, 65, 66, 70-77, embracing particularly on an immunization method of any polyepitope encoded DNA vaccine or immunogenic composition to a virally infected human patient or a human at risk of a viral infection, *e.g.,* specifically humans patient suffering from, or at risk of a condition selected from HIV, hepatitis, exophytic condyloma, flat condyloma, cervical cancer, respiratory papilloma, conjunctival papilloma, genital-tract HPV infection, cervical dysplasia, high grade squamous intraepithelial lesions, and anal HPV infection (Claims 61, 62, 70-73, 76-77) are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims drawn to non-human mammals. The specification does not reasonably provide enablement for any other claimed embodiment directed to human patients, whereby a therapeutically and/or prophylactically treatment effect is contemplated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, particularly when the claims recite specifically that the claimed DNA immunogenic composition in any polyepitope form can be used without any undue experimentation so as to induce a beneficial and/or protective immune response in the human subject as contemplated by the as-filed specification.

With respect to methods of expressing MHC class I or MHC class II binding epitopes at any target site of any human patient or subject within the context of the claimed invention, the specification does not provide sufficient guidance and/or evidences for one skilled in the art to reasonably extrapolate, without undue experimentation, from a simple murine model of transgenic HLA-A *0201/H2Kb mice showing CTL responses generated as a result of intramuscular injection

of microspheres encapsulating DNA encoding a polyepitope HPV polypeptide to any other claimed embodiment as embraced by the breadth of claimed invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention which contemplates that any of the disclosed DNA constructs would exhibit a therapeutically immune effect in any mammal including a human (see claim 61), and more particularly with human patients suffering from, or at risk of having an exophytic condyloma, flat condyloma, cervical cancer, respiratory papilloma, conjunctival papilloma, genital-tract HPV infection, cervical dysplasia, high grade squamous intraepithelial lesions. The state of the art exemplified by McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) indicates:

- "The route of deliver of the DNA vaccine can have an impact on the efficiency of transfection as well as the types and location of cells transfected, and thu8s potentially on the nature of the immune response" (page 295, column 1 bridging column 2);
- "More recent with antigen-encoding plasmids have shown that antigen expression does not continue indefinitely, but rather is lost by some immune-mediated mechanism around 2-3 weeks after DNA injection" (page 295, column 2, last paragraph); and
- A number of factors appear to influence the Th bias of the immune response, including (i) the angigen; (ii) the dose of antigen; (iii) whether the antigen is secreted, cytoplasmic, or membrane bound; (iv) the route and method of DNA administration; (v) the number of immunizations; (vi) the presence of CpG motifs; (vii) the haplotype of the mouse immunized; (viii) the presence of adjuvant; (ix) co-expression of cytokines; (x) whether DNA is formulated (e.g., with cationic liposomes); and (xi) rest period between immunizations (page 296, column 1).

Even if an animal model including a mouse model may show a desire immune response (CTL responses) by art-recognized intramuscular injection route, McCluskie *et al.* teach that "the

realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human [emphasis added] will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition and as to mucosal routes as embraced by the claims, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

More specifically as to the challenges in DNA vaccine for use in human patients, Pachuk *et al.,* Current Opinion in Molecular Therapeutics, Vol. 2, No. 2, 2000, pp. 188-198, states (page 188, abstract):

> Vaccination with DNA is a recent technology possessing distinct advantages over traditional vaccines...DNA vaccines can be manufactured and formulated by generic processes.
>
> DNA vaccine technology, however, is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans [*emphasis added*];

With respect to mucosal immunization including direct administration of a DNA vaccine to a mucosal tissue, Pachuk states on page 192, column 1, fourth paragraph:

> While a great deal of research continues in the area of mucosal DNA immunization, it is clear that much remains to be learned and that administration of DNA through multiple sites may be necessary to achieve protective immunity.

Pachuk then concludes on page 195:

In conclusion, the potential of plasmid DNA-based vaccines has sparked enormous activity in DNA delivery research....Advances in controlled self assembly of DNA complexing agents, novel carriers for oral, skin and lung administration are expected in the near future. Intradermal inoculations have shown promise in several animal species for certain antigens. However, [emphasis added] the rules that govern why certain antigens and certain sites perform differently from others is unclear. Further research is expected to clarify these issues as well as to develop a clear understanding of the cell types involved. Unraveling the intracellular pathways that need to be invoked to assure robust immune response through chemokines, costimulatory molecules and antigen delivery should also allow rational design of delivery vehicles for plasmid DNA vaccines.

Another skilled artisan, McKenzie, Immunologic Res. 24/3:225-244, 2001, states:
As DNA or RNA vaccines may induce both cell-medicated and humoral immunity, great interest has been shown in them. However, doubt remains whether their efficacy will suffice for their clinical realization (abstract);

Enhanced mucosal and systemic cellular and humoral responses in mice have been induced through mucosal delivery of DNA with monophosphoryl Lipid A, a non-toxic derivative of LPS (173). Similar effects were found with codelivery of saponin adjuvant QS-21 with an intranasal DNA vaccine (174). However, the long and unspectacular history of oral delivery of protein vaccines should caution that the task for these formulations to reach success remains formidable. (page 236, column 2)

The task ahead is to achieve a quantum leap in immune responses in human s in both cellular and antibody response (page 237, column 2);

It is sobering to note that the hepatitis B vaccine took 25 years to develop (187). Perhaps the jury on DNA vaccines and whether we can overcome their weak efficacy will take another 10 years (page 238, column 1 bridging column 2).

Thus and notwithstanding the fact that there is the lack of any prior art to provide any

substantial evidence to demonstrate that it is reasonably predictable to employ a HPV DNA vaccine in therapeutic and/or prophylactic treatment of human patient suffering from or at risk of having an HPV infection or disorders associated with an HPV infection, and that there if the lack of reasonable correlation between the as-filed specification and the non-enabling claimed embodiments, the claimed invention also embrace an immunization of any human patient including those of being at risk of being infected by an HIV virus. In this regard, In addition to the art of record cited in the preceding paragraph with respect to the state of the art of HIV-treatment, Piscitelli, The Annals of Pharmacotherapy, Vol. 30:62-76, 1996, states:

> Despite enormous strides in our understanding of HIV pathogenesis at the cellular and tissue levels, this knowledge has yet to be translated into clinical treatment options that are of comparable magnitude. Fifteen years into the pandemic, the therapy of HIV infection continues to rely heavily on the use of a relatively small number of antiretroviral agents such as the nucleoside analogs (either singly or in combinations), whose influence on disease progression is modest at best. (page 63, column 1).

> Immune based approaches may be a double-edged sword. By enhancing immune function, they possess the potential to extend survival. However, they also may induce HIV replication by stimulating the proliferation of HIV-infected cells. Long-term studies examining viral burden and survival eventually will answer these questions. (page 73, column 1).

Cohen and Fauci, JAMA, Vol. 280, Vol. 280, No. 1: 87-88, 1998, reviewed the state of the art of anti-HIV therapy in human patients in the past and indicates:

- The need to induce humoral (antibody), cellular (cytotoxic T lymphocyte-mediated), and mucosal (preventing viral entry at mucosal surfaces) immunity.
- HIV resides in immunoprivileged sites and can remain latent for years.
- HIV causes immunosuppression, further hindering the body's ability to contain the virus and prevent opportunistic infections.
- How the virus destroys immune cells is not fully understood.

- No good animal model exists.
- HIV continuously mutates: different strains are prevalent in various parts of the world; field isolates often differ from the laboratory strains used to develop vaccines; and after infection, HIV can mutate within the host, and an infected person can harbor multiple forms of the virus.
- The appropriate clinical end points for evaluating therapeutic vaccines are not clear.

Cohen and Fauci in summary states that "the development of a safe and effective vaccine continues to encounter a host of sobering challenges, including geographic variability of HIV subtypes, and the lack of correlates of protective immunity in HIV infection (page 88, column 1).

In view of the reasonable unpredictability of the state of the art of DNA immunization methods for any human patients as indicated in the totality of the prior art as exemplified above, one skilled in the art then turns this instant specification for guidance, however, other than simple CTL responses generated in transgenic mice which is not even a real-world mammal intended for the contemplated utility, as the result an intramuscular injection of microspheres encapsulating plasmid vectors encoding HPV epitopes, the specification does not provide sufficient guidance and/or evidence to overcome the obstacles as disclosed in the state of the prior art.

Even if a partially protective and/or therapeutic response has been shown in mice using the exemplified protocol, it is not apparent as to how the murine model using one single species of HPV encoded plasmid encapsulated in microspheres is reasonably extrapolated to the full scope of the claimed invention including a human subject at risk or being infected by any pathogenic pathogen, particularly given that there is no evidence that the murine model is a general phenomenon for any other claimed embodiment, and given the doubts expressed in the art of record.

The only *Wands* factor that has been met by the as-filed application is that the skill of a person skilled in the art of DNA vaccine is relatively high, however, the skilled artisans, particularly on the basis of the prior art of record, remain, at the time the invention was made, actively involved in further experimentation of finding out solutions and/or particular types of carriers so as to overcome the barriers and/or the lack of reasonable predictability in practicing any DNA vaccine in human subjects as claimed. The only novel contribution on the basis of the

as-filed specification is the concept of employing a polyepitope encoded DNA construct in a DNA vaccination method, however, neither the as-filed specification provide any solution so as to overcome the doubts expressed by the art of record in performing any DNA vaccine and/or therapeutically immunogenic composition in any human patient as broadly claimed, nor does the as-filed specification provide any guidance and/or factual evidence as to how to lead one skill in the art, without any undue experimentation, to determine as to which carriers and/or microsphere/microparticle from the prior art would be prophylactically and/or therapeutically effective within applicant's context of the claimed invention, nor does the as-filed specification provide any guidance so as to reasonably extrapolate from a simple murine model to an efficacy in any human subject as generically claimed, particularly in view of the requirement of the *Wands* factors which has not been sufficiently met by the as-filed specification, and in view of the totality of the art of record regarding the state of the DNA vaccine art and/or therapeutically immunogenic DNA composition in human subjects.

Note also that the court decisions cited in In re Wright, (CA FC) 27 USPQ2d 1510 (1993), Enzo Biochem Inc. v. Calgene Inc., 188F .3d 1362, 1374, 52 USPW2d 1129, 1138 (Fed. Cir. 1999). See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997):

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a genetic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable of the public to understand and carry out the invention.").

In addition and as analogously explained in In re Wright, (CA FC) 27 USPQ2d 1510 (1993), the claims are directed to methods of using DNA vaccines in a human at risk of being infected by any viral infection including an HPV infection, which must by definition trigger a therapeutic or an immunoprotective response in the vaccinated or immunized human; mere antigenic response or a simple detection of an transient antibody response is not enough. In addition, Appellants attempt to claim in the claims of *any* DNA vaccine encoding *any* HPE polyepitope. In fact, in Wright's case, the court decision states:

> [M]many of the appealed claims encompass vaccines against AIDS viruses and

> that, because of the high degree of genetic, antigenic variations in such viruses, no one has yet [even in 1993 when the court decision was made], years after his invention, developed a generally successful AIDS virus vaccine" (page 1513);

The following references are further cited to indicate that lack of reasonable predictability of DNA vaccine in human subjects:

> Richardson, Journal of General Virology, 83:2515-2521, 2002.

Thus, it is not apparent how one skilled in the art, without undue experimentation, practices the full scope of the claimed invention, and/or uses the DNA immunization methods as claimed to provide an active immunity for any future protection and/or therapeutic efficacy against an infection by any and/or strains of a pathogenic organism in any human patient, particularly on the basis of applicant's disclosure, and in view of the doubts expressed in the art of record at the time the invention was made.

Applicant's response (filed April 21, 2003, page 14) has been considered by the examiner but is not found persuasive for the reasons of record.

In view of the latest submitted IDS and the prior art relevant to the cited reference in the IDS being found by the examiner, the species restriction of record is reinstated and the following rejection is applicable.

Claims 1-40, 52-60, 64-66, 68, 74-75, drawn to a generic invention as set forth in the base claims and claims dependent there from, are rejected under 35 USC 103(a) as being unpatentable over either Gajewczyk (US Pat No. 6,235,523) or Hedley *et al.* (US Pat No. 5,783,567), taken with either Fikes (US Pat No. 6,534,482 B1) or BOT (US 2002/0103145 A1).

With respect to the generic claims, Gajewczyk (columns 3-5) and Hedley *et al.* a method of eliciting an immune response in a mammal, the method comprising administering to the mammal an effective amount of microspheres comprising a polymeric matrix or shell and a nucleic acid encoding a trafficking signal sequence and polyepitopes of HPV, wherein the nucleic acid encodes a hybrid polypeptide comprising a targeting signal sequence and polyepitopes of naturally occurring pathogenic proteins, wherein the epitopes are either contiguous or are separated by a spacer amino acid or spacer peptide)

and wherein the nucleic acid encodes at least a HPV epitope of at least 11 amino acids in length (Hedley *et al., e.g.,* columns 2, 6, 13, 14, 61-64; claims in Gajewczyk).

Hedley *et al.* or Gajewczyk does not teach the specific combination of at least 6 HPV epitopes, which are derived from three different pathogenic proteins from at least one pathogenic agent, *e.g.,* HPV.

However, at the time the invention was made, the concept of employing HPV polyepitope encoding vector is well recognized in the prior art as exemplified in Fikes and BOT. More specifically, Fikes teaches on column 20, last paragraph, that the minigenes are comprised of two or many different epitopes (see.e.g., Table 1-8). On column 40, DNA encodings 9 epitopes was discloses and shown to be effective in inducing significant CTL response. Similarly, BOT teaches on pages 3-5. particularly page 4 bridging page 5, he advantages of synergism of making and use of a DNA immunogenic composition comprising one or more DNA constructs encodings multi-epitopes from different antigenic proteins. Furthermore and as evidenced by Gajewczyk, a vector for DNA immunogenic composition, which comprises 4 distinct epitopes of HPV-16 E7 and one epitope of HPV-16 E6, is exemplified and shown to be an effective immunogenic composition for inducing an immune response *in vivo.*

As such, it is apparent from the state of the totality of the prior art that the concept of employing DNA immunogenic composition comprising numerous epitopes from a combination of distinct antigenic proteins derived from pathogenic agent is well-recognized and embraced by those of ordinary skill in the art. As such, It would have been obvious for one of ordinary skill in the art at the time the invention was made to have employed any combination of HPV epitopes available in the prior art such as those disclosed in Fikes and Gajewczyk in the DNA immunization methods of Hedley *et.* or Gajewczyk so as to increase an immune response against any viral infection including HPV in any target mammal. One of ordinary skill in the art would have been motivated to have employed the combination as recited in the elected species because the combination of the known epitopes are minor modifications and within the available recombinant DNA techniques and expected to provide an addictive effect in increasing an immune response against HPV in a target mammal, as taught by the combined cited references.

One of ordinary skill in the art would also have been motivated to employ any particular combination and number of epitopes derived from distinct pathogenic proteins in the immunization methods of the combined cited reference, which includes the combination of 6

epitopes, wherein 2 epitopes of which are derived from a distinct pathogenic protein. One of ordinary skill in the art would have been motivated to employ such combination as a matter of design choice and minor modifications, since the totality of the prior art does teach that as long as a combination of polyepitopes is employed, and that the more are the better in term of addictive effects and potential synergistic effects.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1-44, 46--60, 64-66, 68, 74-75, drawn to the elected species designated as the combination of SEQ ID NO: 66, SEQ ID NO: 69, SEQ ID NO: 152, and SEQ ID NO: 154, microspheres containing a nucleic acid sequence encoding the combination of sequences of SEQ ID NO: 66, 69 152 and 154, and intramuscular administration of the nucleic acid sequences or the microspheres, are rejected under 35 USC 103(a) as being obvious over either Gajewczyk (US Pat No. 6,235,523) or Hedley *et al.* (US Pat No. 5,783,567) taken with either Fikes (US Pat No. 6,534,482 B1) or BOT (US 2002/0103145 A1), and further in view of any of Boursnell *et al.* (US pat No. 5,719,054) or Boursnell *et al.* (US pat No. 5,719,054), Edwards *et al.* (US Pat No. 6,004,557), Dillner *et al.* (US Pat No. 5,932,412) and Bleul *et al.* (US Pat NO. 5,753,233).

The rejection of the base claims and/or generic invention drawn to the concept of employing a DNA immunogenic composition comprising a DNA vector encoding a polyepitope and/or combination of various epitopes, is applied as indicated above

With respect to the specific HPV epitopes and/or combination of epitopes of HPV that were elected for examination, Boursnell *et al.* teach the HPV epitopes comprising SEQ ID NOS: 66, 69, 152, and 154 in SEQ ID NOS: 9 (comprising SEQ ID NO: 69), 10 (comprising both SEQ ID NOS 66 and 152) and 13 (comprising SEQ ID O: 154). Furthermore, Edwards *et al.* (US Pat No. 6,004,557), Dillner *et al.* (US Pat No. 5,932,412) and Bleul *et al.* (US Pat NO. 5,753,233) are exemplified references that discloses the immunoreactive HPV epitopes of SeQ ID NOS 66, 69, 152, and 154, respectively in SEQ ID NO: 12 (Edwards *et al.*), SEQ ID NO: 157 (Dillner *et al.*), SEQ ID NO: 2 (Bleul *et al.*) and SEQ ID NO: 61 (Dillner *et al.*).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to have employed any combination of HPV epitopes available in the prior art such as those disclosed in Boursnell *et al.* and or in Boursnell, Edwards *et al.* (US Pat No. 6,004,557), Dillner *et al.* (US Pat No. 5,932,412) and Bleul *et al.* (US Pat NO. 5,753,233) in the DNA immunization

methods of taught by Hedley taken with Fikes or BOT so as to increase an immune response against HPV in any target mammal. One of ordinary skill in the art would have been motivated to have employed the combination as recited in the elected species because the combination of the known epitopes are minor modifications and expected to provide an addictive effect in increasing an immune response against HPV in a target mammal, as taught by Gajewczyk (US Pat No. 6,235,523) or Hedley *et al,* taken with Fikes and BOT, and because Boursnell *et al.,* Edwards, Dillner *et al.* and Bleul *et al.* all teach that the epitopes comprising SEQ ID NOS 66, 69, 152 and 154 are immunoreactive to antibodies against HPV.

Thus, the claimed invention as a whole was *prima facie* obvious.

The no statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a no statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-44, 46--60, 64-66, 68, 74-75, embracing the elected species designated as the combination of SEQ ID NO: 66, SEQ ID NO: 69, SEQ ID NO: 152, and SEQ ID NO: 154, microspheres containing a nucleic acid sequence encoding the combination of sequences of SEQ ID NO: 66, 69 152 and 154, and intramuscular administration of the nucleic acid sequences or the microspheres, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-81 of U.S. Patent No. 6,183,746, taken with Gajewczyk (US Pat No. 6,235,523) or Hedley *et al.* (US Pat No. 5,783,567), taken with either Fikes (US Pat No. 6,534,482 B1) or BOT (US 2002/0103145 A1), and further in view of any, Boursnell *et al.* (US pat No. 5,719,054) or Boursnell *et al.* (US pat No. 5,719,054), Edwards *et al.* (US Pat No. 6,004,557), Dillner *et al.* (US Pat No. 5,932,412) and Bleul *et al.* (US Pat NO. 5,753,233).

Although the conflicting claims are not identical, they are not patentably distinct from each other because .

US Patent No. 6,183,746 claims a method of eliciting an immune response in a mammal, the method comprising administering to the mammal an effective amount of microspheres comprising a polymeric matrix or shell and a nucleic acid encoding a trafficking signal sequence and an HPV epitope.

US Patent No. 6,183,746 does not claim the specific combination of HPV epitopes designated as SEQ ID NOS: 66, 69, 152 and 154 for use in the making the HPV polyepitope encoding plasmid containing microspheres.

However, at the time the invention was made, the concept of employing HPV polyepitope encoding vector is well recognized in the prior art as exemplified and indicated above. Plasmid vectors expressing polyepitope fragments of pathogenic proteins and complexes with microspheres are also taught in Gajewczyk (US Pat No. 6,235,523) or Hedley *et al.* In fact Boursnell *et al.* teach the HPV epitopes comprising SEQ ID NOS: 66, 69, 152, and 154 in SEQ ID NOS: 9 (comprising SEQ ID NO: 69), 10 (comprising both SEQ ID NOS 66 and 152) and 13 (comprising SEQ ID O: 154). Furthermore, Edwards *et al.* (US Pat No. 6,004,557), Dillner *et al.* (US Pat No. 5,932,412) and Bleul *et al.* (US Pat NO. 5,753,233) are exemplified references that discloses the immunoreactive HPV epitopes of SeQ ID NOS 66, 69, 152, and 154, respectively in SEQ ID NO: 12 (Edwards *et al.*), SEQ ID NO: 157 (Dillner *et al.*), SEQ ID NO: 2 (Bleul *et al.*) and SEQ ID NO: 61 (Dillner *et al.*).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to have employed any combination of HPV epitopes available in the prior art such as those disclosed in Gajewczyk, Boursnell *et al.* and or in Boursnell *et al.* taken with Edwards *et al.* (US Pat No. 6,004,557), Dillner *et al.* (US Pat No. 5,932,412) and Bleul *et al.* (US Pat NO. 5,753,233) in the DNA immunization methods of as claimed in Collins *et al.* so as to increase an addictive immune response against HPV in any target mammal. One of ordinary skill in the art would have been motivated to have employed the combination as recited in the elected species because the combination of the known epitopes are minor modifications and expected to provide an addictive effect in increasing an combination of immune responses against HPV in a target mammal, as taught by Gajewczyk (US Pat No. 6,235,523) or Hedley taken with Fikes or BOT., and because

Boursnell *et al.*, Edwards, Dillner *et al.* and Bleul *et al.* all teach that the epitopes comprising SEQ ID NOS 66, 69, 152 and 154 are immunoreactive to antibodies against HPV.

Thus, the claimed invention as obvious variants of that of the Collins *et al.* patent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

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Primary Examiner
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DAVE T. NGUYEN
PRIMARY EXAMINER